REMARKS

First, applicants appreciate the willingness of the Examiner to consider the Information Disclosure Statement submitted 21 November 2001. Applicants also appreciate the withdrawal of a number of grounds for rejection previously made.

All of the outstanding grounds for rejection have the same basis, the combination of Kyriazis, *et al., Cancer Res.* (1981) 41:3995-4000, in view of Otto, *et al., J. Urol.* (1985) 134:170-174, Wang, *et al., Exp. Cell. Biol.* (1982) 50:330-331 and McLemore, *et al., Cancer Res.* (1987) 47:5132-5140. Kyriazis and Otto are said to teach successful production of tumor mimics, including metastases, in nude mice when intact tumor samples were implanted subcutaneously; Wang and McLemore are said to teach the advantage of orthotopic implantation of cell suspensions.

The Office maintains that one of ordinary skill would have been motivated to modify the procedures of Kyriazis and Otto to implant the tumors orthotopically in view of the putative teaching of Wang and McLemore that orthotopic implantation of cell suspensions provides good results. The Office further maintains that it would be expected that the results described and claimed by applicants would result from this combination. Respectfully, for the reasons that follow, applicants submit that the cited documents do not provide a motivation for their combination and that the combination, once made, does not predict the highly successful results of the present invention.

Kyriazis describes planting pieces of intact tumor of various types subcutaneously into nude mice. As shown in Table 1 of the document, the implants were tested for both local invasion and metastases. It is noted that Table 1 shows the results only for lymph nodes and lung; however, it is evident that other tissues were tested by Kyriazis in view of the disclosure on page 3996 that certain pancreatic-derived carcinomas metastasize to the diaphragm. While the

Office is correct that Kyriazis makes the statement that these tumors "show overt malignant behavior recapitulating the biological characteristics of the tumor of origin," it is respectfully submitted that the data provided by Kyriazis fail to demonstrate that this is the case. This is perhaps most dramatically shown in the case of bladder cancer where Kyriazis tested for bladder cell line-derived tumors. As shown in the enclosed declaration of Dr. Robert Hoffman, the clinical pattern of metastasis of bladder cancer is known to involve regional lymph nodes, liver, lung, pancreas, diaphragm and spleen citing Holland, James E., *et al.*, Cancer Medicine; 5th ed., B.C. Decker, Inc. (2000) chapter 107. The results of Kyriazis for the tumor derived from SW800 and SW780 cell lines showed only metastasis to the lymph nodes and diaphragm and lungs. Not only was the clinical pattern incompletely observed in these cases, *no metastasis at* all was observed when the tumor was derived from the RT4 cell line and the findings from tumors derived from the 13678 cell line were characterized by Kyriazis as inconsistent.

On the other hand, as set forth in Dr. Hoffman's declaration, the nude mouse model of the invention showed metastasis, as would occur in the clinic to the liver, pancreas, diaphragm, omentum, iliac lymph nodes, superficial inguinal lymph nodes and gastric lymph nodes as described in the published report Fu, X., *et al., Int. J. Cancer* (1992) 51:989-991.

Similarly, with respect to colon cancer, Kyriazis tested tumors derived from the SW480 cell line and found metastases only in the lymph nodes and lungs. It is known from clinical studies as described by Holland (*supra*) at chapter 103 that colon cancer metastasizes to the liver, mesenteric lymph nodes, omentum, peritoneum, lung, and abdominal wall, and exhibits disseminated carcinomatosis. Clearly the clinical pattern is incomplete in Kyriazis' method. The present applicants, on the other hand, have demonstrated, using their method, metastasis to the liver, peritoneum, mesenteric lymph nodes, lung, omentum, abdominal wall and ileum as

described in Fu, X., *et al., Anticancer Res.* (1992) 12:1395-1398; Togo, S., *et al., Cancer Res.* (1995) 55:681-684; An, Z., *et al., Clin. Exp. Metastasis* (1997) 15:184-185.

The results for Kyriazis' testing of pancreatic cell lines are not much better; metastases were demonstrated only to the axillary lymph nodes and lung for the (Mia)PaCa and Capan-1 derived tumors whereas it is known from Holland, J.E. (*supra*) chapter 101, that in the clinic metastases occur to liver, spleen, portal lymph nodes, colon, stomach, mediastinum, lung, kidney, retroperitoneum, diaphragm and small intestine. Applicants have been able to demonstrate metastases to these locations for several pancreatic cell line-derived tumors, for example, in the paper by Bouvet, M., *et al., Clin. Exp. Metas.* (2000) 18:213-218; Lee, N.C., *et al., Clin. Exp. Metas.* (2001) 18:379-384; Bouvet, M., *et al., Cancer Res.* (2002) 62:1534-1540, where for the same (Mia)PaCa cell line-derived tumors, metastases were found in the liver, spleen, portal lymph nodes, stomach, mediastinum, lung, and retroperitoneum.

Similarly, breast cancer is known to metastasize to the axillary lymph nodes, lung, liver and bone (Holland, J.E. (*supra*) chapter 118). The BrCa cell line-derived breast tumor was found by Kyriazis to metastasize only to the lymph nodes (and not to the lung, although this was tested); applicants have shown that their model results in metastasis to the axillary lymph nodes, lung, liver and bone as described by Li, X-M., *et al., Clin. Exp. Metas.* (in press), An, Z., *et al.,* unpublished results set forth in Dr. Hoffman's declaration).

Thus, the Kyriazis model, which involves subcutaneous implantation of intact tumor samples was not, in fact, successful in "recapitulating the biological characteristics of the tumor of origin." It is unclear that Kyriazis might have meant by this statement in view of the clear failure of the results to recapitulate the clinical metastases observed for the corresponding tumors.

Otto is cited as describing the results when tumor pieces were transplanted subcutaneously into nude mice as "correlating well with the clinical course of the patients." First, applicants do not find this statement in the cited document; this statement is made in a different paper by Otto which is described as the basis for the cited paper - Otto, U., *et al.*, *J. Urol.* (1984) 131:130-133. However, Otto did not observe any metastasis even though it is known that renal cell carcinoma, the tumor used by Otto metastasizes to the lung, lymph nodes, liver and brain (Holland, J.E. (*supra*) chapter 1057). Metastases to lung, lymph nodes and liver was demonstrated by the current applicants as described by An, Z., *et al., Clin. Exp. Metas.* (1999) 17:265-270.

In point of fact, the statement in Otto referred to by the Office does not discuss the progress of the disease at all, but rather "the growth rate of these tumors after transplantation" (Abstract on page 130). The Otto paper is entirely silent on metastasis and is focused only on whether the tumor "takes" and is able to grow at all in the mouse. Thus, Otto does not even suggest using the method described as a method to follow the progress of the tumor taken as a clinical whole.

The foregoing shows the unexpected and superior results of the invention method compared with the relatively dismal correlations found by Kyriazis to the overall progress and metastasis of tumors as they develop in a clinical setting in a nude mouse model.

There is no assertion, of course, that the methods or the rodent models claimed by applicants are in any way anticipated by either Kyriazis or Otto; clearly they are not since the model is inherently different. There is also no assertion that Kyriazis or Otto alone or together render the present claims obvious alone without more documentation or suggestion. The Office cites Wang and McLemore for the proposition that these documents teach that orthotopic implantation of tumors provides superior results to subcutaneous implantation in providing

model systems. Applicants respectfully submit that neither Wang nor McLemore provides such a teaching, that there is no motivation to combine what Wang and McLemore do teach with Kyriazis and/or Otto, and that even if these documents are combined, they do not lead to a reasonable expectation of the results obtained by applicants.

The Office asserts that Wang, at page 331, teaches that "Orthotopic transplantation of colonic tumors maintained in nude mice into the colonic wall of naïve nude mice results in growth and metastasis of colonic tumors which mimics the pattern of metastasis observed in human patients." Respectfully, this is not exactly what Wang says. What Wang says is "colonic tumors invaded the various subregions of the colonic wall and mimic the original pattern characteristic for patient tumors." Nothing is said concerning the progress of the disease or metastasis. The succeding sentence "A propensity for tumor cells to growth within lymphatics and to a lesser degree in veins was observed" is unclear as to its reference point. The abstract goes on to say that "Kinetic data suggests that gut implanted tumors were initiated from a small number of injected cells, but there was no significant difference in the labeling indices obtained after ^{3}H-thymidine I.V. administration between s.c. and gut grafted tumors once established in their respective sites." This latter sentence would imply that the site of implantation makes no difference. And the next sentence would indicate that gut implanted tumors are less aggressive "Initial tumorigenic cell dose as well as local cell loss factor may account for a *smaller size* of gut-vs. s.c.-implanted tumors as given time intervals."

A reading of Wang would convey to the reader, first, that it is unclear exactly what Wang did in the first place, and second that it is less than a ringing endorsement for orthotopic implantation.

McLemore is not a great deal better. McLemore describes, as the Office correctly states, that several different human lung carcinoma cell lines were implanted intra-bronchially - *i.e.*, an

orthotopic injection of such cells. The Office then states that McLemore demonstrates that "mice transplanted intra-bronchially with lung tumor cells demonstrated increased rates of growth and metastases than those transplanted subcutaneously" citing the abstract and Table 1. Again, respectfully, this is not exactly true. The abstract merely says that "organ specific *in vivo* implantation of human tumors facilitates optimal tumor growth" without commenting on overall progress of the disease or metastasis. As a matter of fact, the abstract also states that "most (>90%) of the lung tumors propagated by intra-bronchial implantation were localized to the right lung fields as documented by necropsy . . ." (and thus not metastasized). Table 1 does not appear to show any superior results at all. First, the primary cell types implanted were not, for the most part, orthotopic. In the case of the orthotopic implantation intra-bronchially of bronchioloalveolar primary tumor cells, actually, only one out of three implants worked at all. The metastatic tumors implanted were not even bronchioloalveolar but were rather prostate or bladder tumor cells and thus are irrelevant to determining whether orthotopic implantation is helpful. And the paragraph on page 5136 discussing the implantation of human lung tumor cells, states that necropsy showed that 91% of the tumors implanted by this method were *localized* to the right lung; only 3% of the implanted tumor-bearing animals had distant metastases. The discussion on page 5139 implies that orthotopic implantation is helpful, but certainly does not plainly say so, and the results hardly demonstrate that an accurate model of the human disease would be obtained.

Thus, one reading McLemore would not conclude that implantation of tumors orthotopically would provide any kind of a model for metastasis. In sum, the teachings of Wang and McLemore are considerably more muted that the Office has asserted.

This is in contrast to the results obtained using the claimed invention method. For example, in the article by Yang, M, *et al., Cancer Res.* (1998) 58:4217-4221, attached to Dr.

Hoffman's declaration, eight nude mice implanted in the left lung by surgical orthotopic implantation with intact cubes of lung tumor tissue all showed metastasis to the contralateral lung and chest wall and seven showed metastasis to the skeletal system. (See page 4218, top right-hand column.) In addition, the paper by Rashidi, B, *et al., Clin. Exp. Metas.* (2000) 18:57-60 shows that the surgical orthotopic implantation of lung carcinoma in 10 mice showed extensive metastases (see page 60, left-hand column).

As to the second aspect of this discussion, it is difficult to find any motivation for combining either or both Kyriazis and Otto with either or both of Wang and McLemore. Certainly there is nothing in Kyriazis or Otto that suggests that the implantation might be orthotopic rather than subcutaneously and certainly there is nothing in either Wang or Otto that suggests that intact tumor pieces should be used in lieu of tumor cells. There is no common problem to be solved, either. True, all of the documents have to do with providing tumor models, but none appears to recognize that there is inadequacy in the demonstration of metastasis using the models provided. None presents any problem to be solved. And, of course, the third criterion for combination of documents recognized by *In re Rouffet*, 47 USPQ2d 1453 (Fed. Cir. 1998) - *i.e.*, the notorious nature of one or more of the documents is not found here. Thus, there appears to be no motivation, absent the teaching of the invention, to combine these documents.

Finally, even if the documents were combined and somehow rendered the present invention obvious to try, there is no reasonable expectation of the results obtained. The Office asserts that the unexpected results obtained by the methods of the invention and exhibited by the claimed models are not recited in the claims. It is respectfully submitted that this is unnecessary. The claims set forth the required steps in the method and the structural characteristics of the resultant thereof. There is no legal requirement of which applicants are aware that the claims

recite anything other than these features. Unexpected results will support a finding of patentability irrespective of whether they are specifically set forth in the claims.

And there has been ample demonstration of the unexpectedly successful results of the methods and models of the invention. This is explicitly set forth, for example, in the enclosed declaration of Dr. Robert Hoffman.

For the reasons stated above, it is believed that all of the pending claims are clearly patentable over the cited art. Applicants do not question the applicability of the invention to rats and SCID mice as taught in the tertiary references; claims with these limitations are patentable for the same reasons as claims directed to nude mice.

CONCLUSION

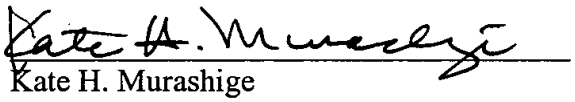
None of the documents cited suggest the method of the invention which requires orthotopic implantation of intact tumor pieces to provide models of progression and metastasis as would be exhibited in the clinical progression of human tumors. There is no assertion that either the methods or the resulting models are anticipated by the documents of record. Neither are the methods and models rendered obvious thereby. The primary references which describe subcutaneous implantation of tumor pieces show that this model fails to mimic human tumor progression, including metastatic progression but fail to recognize that this is problematic (Kyriazis) or are not concerned with the overall progress of tumor growth but rather whether tumors "take" (Otto). The secondary references are either undecipherable as to what was actually done and what the results were (Wang) or show that orthotopic implantation of lung tumor cells fails to exhibit metastasis at all. No document suggests that there is anything wrong with the model proposed therein or provides any incentive to combine it with another document. Once combined, the documents fail to suggest the results obtained by applicants and demonstrated in published reports and by declaration as well as in the specification. There is no

documentation of record that even if one were motivated to try the method of the invention, the highly successful and dependable results demonstrated would be expected or obtained. Accordingly, the patentability of the methods and models of the invention is supported by the lack of a *prima facie* case of obviousness and by unexpected results as well. Accordingly, withdrawal of the rejections and passage of claims 1-18, 20-25, 27-28, 30-37, 42-49 and 54-61 to issue is respectfully requested.

In the unlikely event that the transmittal letter is separated from this document and the Patent Office determines that an extension and/or other relief is required, applicants petition for any required relief including extensions of time and authorize the Assistant Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to **Deposit Account No. 03-1952** referencing docket No. 312762001530.

Respectfully submitted,

Dated: May 13, 2002

By: 

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